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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For The

NEOACIDS C5-C28 CATEGORY

CAS# 75-98-9: Propanoic acid, 2,2-dimethyl-
CAS# 598-98-1: Propanoic acid, 2,2-dimethyl-, methyl ester
CAS# 95823-36-2: Carboxylic acid, C6-8 neo
CAS# 26896-20-8: 2,2-Dimethyloctanoic acid
CAS# 68938-07-8: Fatty acids, C9-C13 neo
CAS# 72480-45-6: Fatty acids, C9-C28 neo

Prepared by:

ExxonMobil Chemical Company

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EXECUTIVE SUMMARY

Under EPA's High Production Volume (HPV) Challenge Program ExxonMobil Chemical Company has committed to voluntarily compile a Screening Information Data Set (SIDS) on a category of chemicals defined as Neoacids C5-C28. This category is supported by the basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and human and environmental effects of chemicals as defined by the Organization for Economic Cooperation and Development (OECD). The information used to complete the HPV SIDS endpoints comes from existing data.

ExxonMobil Chemical Company believes a category of Neoacids C5-C28 is scientifically justifiable because their physicochemical and toxicological properties are very similar and follow a regular pattern as a result of the synthesis process. The structural similarities create a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. The similarities are based on the following:

- A common structure represented by R3CCOH,
- An incremental and constant change in carbon number across the category where the total number of carbons represented by R ranges from 3 to 26, and
- A likelihood of common precursors and breakdown products that can result in structurally similar metabolites (e.g. carboxylic acid).

This test plan is based on the observation that the toxicological properties are similar or vary in an incremental and predictable fashion within the category.

The test data compiled for the category anchor studies proves adequate to support a screening-level hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6). The untested endpoints can be assessed by interpolation between data from the category anchor studies.

To complete the hazard assessment of the category, Ames, micronucleus, and algal toxicity studies will be completed on both low and high molecular weight members of the category (75-98-9 and 72480-45-6 or 68938-07-8). Also, a fish acute and invertebrate toxicity study will be conducted on a high molecular weight member (68938-07-8).

Evaluation of the Neoacids C5-C28 as a category has several advantages. The category can be evaluated by using a matrix of completed anchor studies for various members of the category. By using this approach, the safety of the category can be determined without having to conduct tests for every end-point with every chemical. Not only will this inform the public earlier about any hazards of Neoacids C5-C28, but it will also reduce the number of animals that would be required to evaluate the toxicity of individual members of the Neoacids C5-C28 category.

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TEST PLAN FOR NEOACIDS C_5-C_{28}

I. INTRODUCTION

Under EPA's High Production Volume (HPV) Chemical Challenge Program ExxonMobil Chemical Company has committed to voluntarily compile a Screening Information Data Set (SIDS) on a category of chemicals defined as Neoacids C5-C28. This category is supported by the basic screening data needed for an initial assessment of the physicochemical properties, environmental fate, and human and environmental effects of chemicals as defined by the Organization for Economic Cooperation and Development (OECD). The information used to complete the HPV SIDS endpoints comes from existing data and fulfills an ExxonMobil obligation to the HPV Challenge Program.

ExxonMobil Chemical Company believes a category of Neoacids C5-C28 is scientifically justifiable because their physicochemical and toxicological properties are very similar and follow a regular pattern as a result of the synthesis process. The structural similarity of the component chemicals from these products creates a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. The similarities are based on the following:

- A common structure represented by R3CCOH,
- An incremental and constant change in carbon number across the category where the total number of carbons represented by R ranges from 3 to 26, and
- A likelihood of common precursors and breakdown products that can result in structurally similar metabolites (e.g. carboxylic acid).

This test plan is based on the observation that the toxicological properties are similar or vary in an incremental, predictable fashion within the category.

The test data compiled for the category proves adequate to support a hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6) with the exception of few studies that have been identified as necessary to complete a thorough hazard dataset. Once all data are available, the untested endpoints can be assessed by interpolation between data from the category anchor studies. The existing data suggest that products in the Neoacids (C_5-C_{28}) Category exhibit relatively low toxicity for human health endpoints and moderate toxicity for the environmental health endpoints.

To complete the hazard assessment of the category, Ames, micronucleus, and algal toxicity studies will be completed on the low and high molecular weight members of the category (75-98-9 and 72480-45-6 or 68938-07-8). Also, a fish acute and invertebrate toxicity study will be conducted on a high molecular weight member (68938-07-8).

The data from this category will be used to inform the public about the potential hazards of the Neoacids C5-C28. Developing a data matrix of anchor studies and applying justifiable read across practices will provide a sufficiently robust data set to characterize each endpoint in the HPV Chemical Challenge Program without having to conduct a test for each endpoint and product. This resourceful use of existing data will result in fewer animals needed for testing purposes while adequately assessing the potential hazards of products in the Neoacids C5-C28 Category.

II. CHEMICAL PROCESS AND DESCRIPTION

The Neoacids C5-C28 Category contains a group of neoacid products whose physicochemical and toxicological properties are very similar and follow a regular pattern as a result of synthesis and structural similarity (Table 1). The production of neoacid products involves the reaction between a branched olefin with carbon monoxide and water at elevated temperatures and pressures in the presence of an acid catalyst.

The category also contains propanoic acid, 2,2-dimethyl-, methyl ester (CAS#: 598-98-1). This material is an ester that is rapidly hydrolyzed to the parent neoacid - propanoic acid, 2,2-dimethyl- (CAS#: 75-98-9). Because of this rapid hydrolysis, propanoic acid, 2,2-dimethyl-, methyl ester has properties for health effects, aquatic toxicity, and environmental fate that are consistent with the neoacids.

The structural similarity of chemicals in this category creates a predictable pattern in the following parameters: physicochemical properties, environmental fate and effects, and human health effects. Neoacids are trialkylacetic acids in which each hydrogen on the non carboxyl carbon of acetic acid has been replaced by an alkyl group. The structural features of members of the category are as follows:

- A common structure - a quaternary carbon with the general structure R_3CCOOH,
- An incremental and constant change across the category where R can be a branched alkyl group ranging from CH_3 to C_6H_{13} as the main constituent,
- A likelihood of common precursors and breakdown products which result in structurally similar chemicals.

Table 1. CAS Numbers and Descriptions

CAS Number	Chemical Name
75-98-9	Propanoic acid, 2,2-dimethyl-
598-98-1	Propanoic acid, 2,2-dimethyl-, methyl ester
95823-36-2	Carboxylic acid, C6-8 neo*
26896-20-8	2,2-Dimethyloctanoic acid
68938-07-8	Fatty acids, C9-13 neo
72480-45-6	Fatty acids, C9-28 neo

* = Not currently HPV but included to facilitate category evaluation

The Neoacids C5-C28 category accomplishes the goal of the Challenge Program - to obtain screening level hazard information through the strategic selection of products to be tested within the category. The testing strategy is based on the principle that:

- These products behave in a similar or predictable manner, and
- Interpolation of data can be used to assess the neoacid products for which data are not available.

Procedures to assess the reliability of selected data for inclusion in this test plan are based on the guidelines described by Klimisch et al, 1997.

III. TEST PLAN RATIONALE

A. Physicochemical Data

Physicochemical Data (i.e., melting point, boiling point, vapor pressure, water solubility, and Kow) for selected chemical components in the Neo Acid C5 - C28 Category will be calculated using EPIWIN© model (EPIWIN, 1999), as discussed in the EPA document entitled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program." These data will be presented as ranges, based on the chemical components selected to represent each neoacid product. In addition, measured data for some of these endpoints will also be provided for selected neoacid products where readily available. Where possible, measured and calculated data will be presented together for comparison purposes.

Table 2 lists selected measured physicochemical data (melting point, boiling point, and vapor pressure) as they appear on the material safety data sheets for products in this category. These data are provided with this test plan to further justify these products as a distinct category under the HPV Chemical Challenge Program. Also included are calculated values for water solubility and K_{ow}. As shown by the data in Table 2, the structural similarity of the neoacid products results in a predictable and incrementally increasing pattern of physiochemical properties from the C5 to C9-28 products.

Table 2. Selected Physical Properties of Neoacids (C_5-C_{28})

CAS NUMBER	CHEMICAL NAME	MELTING POINT (° C)	BOILING POINT (° C)	WATER SOLUBILITY mg/L	VAPOR PRESSURE (mm Hg @ 20° C)	Log Kow
75-98-9	Propanoic acid, 2,2-dimethyl- (C5)	9.87	166.9	15,590	1.54	1.5
598-98-1	Propanoic acid, 2,2,-dimethyl-, methyl ester (C6)	21.6	187.8	6,135	0.721	1.94
95823-36-2	Carboxylic acid, C6-8 neo (C7)	37.4	207.8	1,537	0.117	2.5
26896-20-8	2,2-Dimethyloctanoic acid (C10)	48.1	252.1	80	0.0147	3.8
68938-07-8	Fatty acids, C9-13 neo	37 - 76	234 - 291	3.1 - 243	0.001 - 0.046	3.3 - 5.2
72480-45-6	Fatty acids, C9-28 neo	37 - 204	234 - 504	<1 - 243	$<1.7 E^{-12}$ - 0.046	3.3 - 6.0

B. Human Health Effects

The structural similarity of the Neoacids C5-C28 influences both their physicochemical (Table 2) and their toxicological properties (Sections C and D). As a chemical category, the Neoacids C5-C28 have predictable, low-level environmental and health hazards.

ExxonMobil Chemical Company believes the category of Neoacids C5-C28 is scientifically justifiable and that the test data compiled for the category proves adequate to support a screening-level hazard assessment for the category and its members (CAS numbers, 75-98-9, 598-98-2, 95823-36-2, 26896-20-8, 68938-07-8, and 72480-45-6). One can assess the untested endpoints by extrapolation between and among the category members. The proposed category assessment plan is shown in Table 3.

Metabolism

Propanoic acid, 2,2-dimethyl-, methyl ester is rapidly cleaved to Propanoic acid, 2,2-dimethyl-. Due to the stability conferred by the quaternary carbon, Neoacids C5-C28 are relatively resistant to biotransformation and do not readily form bioactive metabolites. Enzymatic removal of the alkyl groups at the quaternary carbon would allow for other metabolic processes to occur. These would likely be mitochondrial beta-oxidation or by cytochrome P450 mediated omega and omega-minus-one oxidation (may be followed by beta-oxidation) to produce acetate. However, since Neoacids C5-C28 are not readily metabolized, they would primarily be eliminated in the urine as glucoronic acid conjugates or by dealkylation (Katz and Guest, 1994).

C. Presentation of Neoacids C5-C28 Category Health Effects Data Associated with the Anchor Studies under the HPV Challenge Program

Acute Oral Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethyloctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
ACUTE ORAL - RAT	= 2000 mg/kg	RA	1860 mg/kg	= 2000 mg/kg	RA	RA

All of the Neoacids C5-C28 have a low order of toxicity to rats via the oral route of exposure (EBSI, 1964). The LD_{50} values for Propanoic acid, 2,2-dimethyl- and 2,2-Dimethyloctanoic acid were 2000 mg/kg. In addition, the LD_{50} for Carboxylic acid, C6-8 neo was 1860 mg/kg. These results demonstrate that members of the Neoacids C5-C28 Category have a consistent, low order of acute oral toxicity.

Acute Dermal Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethylo ctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
ACUTE DERMAL - RABBIT	= 3160 mg/kg	RA	> 3160 mg/kg	> 3160 mg/kg	RA	RA

The Neoacids C5-C28 have a low order of toxicity via the dermal route of exposure (EBSI, 1964). The rabbit dermal LD_{50} for all members of the category was equal to or greater than 3160 mg/kg. This indicates that the members of this category have a consistent pattern of acute toxicity via the dermal route of exposure.

Genotoxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethylo ctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
AMES - S. typhimurium; TA98, 100, 1535, 1537, 1538 ± Activation	T	RA	RA	RA	RA	T
Chromosomal Aberration - In Vitro or In Vivo	T	RA	RA	RA	RA	T

RA Read Across
T Test Proposed

There are no structural alerts to suggest that Neoacids C5-C28 are likely to be genotoxic. However, because there are no data available to assess the genotoxic potential of Neoacids C5-C28, we propose to conduct tests to evaluate this endpoint. First, Ames tests will be conducted on materials at either end of the category (Propanoic acid, 2-2-dimethyl- and Fatty acids, C9-28 neo) to evaluate the mutagenicity of the category. Second, mouse micronucleus tests will be conducted on these same materials to evaluate the clastogenicity of the category. The mouse micronucleus test is widely accepted by regulatory agencies to evaluate clastogenicity. This category approach will minimize the amount of unnecessary animal testing and will maximize the utility of both existing and newly generated data.

Subchronic Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethyloctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
RAT DERMAL	NOAEL (dermal) = 300 mg/kg	RA	NOAEL (dermal) = 553.7 mg/kg	NOAEL (dermal) = 2280 mg/kg	RA	RA

The subchronic toxicity of Neoacids C5-C28 has been assessed by conducting repeat dermal exposure studies. Dermal exposure is the primary route of exposure for Neoacids C5-C28, particularly in an industrial setting. An evaluation of the repeated dose studies indicates that Neoacids C5-C28 have a low order of subchronic toxicity. Propanoic acid, 2,2-dimethyl-, in isopropyl alcohol solution, was repeatedly applied to the shaved intact skin of albino rabbits 5 days/week for two weeks (for a total of 10 applications) at doses of 30 or 300 mg/kg/day (Hazleton, 1964a). Slight to moderate irritation at the low dose and moderate to marked irritation at the high dose was observed. Slight or moderate erythema, atonia, and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, slight to marked edema, moderate or marked atonia and desquamation. Some dermal necrosis at the site of application was seen in three rabbits and persisted throughout the study. Control animals that received only the solvent (isopropyl alcohol) showed slight irritation. There were no signs of systemic toxicity attributable to dermal absorption of propanoic acid, 2,2-dimethyl-. The NOAEL for systemic toxicity in this study was 300 mg/kg.

In a similar study, carboxylic acid, C6-8 neo was applied at 55.4 mg/kg and 553.7 mg/kg for 10 applications (Hazleton, 1964b). No treatment related effects were observed on behavior of clinical signs during the in-life phase of the study. Gross pathology of the animals in all dose groups did not reveal any abnormalities. Repeated application of carboxylic acid C6-8 neo did produce marked skin irritation with some dermal necrosis at the site of application in the high dose group. Since no systemic effects were observed in this study, the NOAEL for systemic effects following subchronic dermal application of carboxylic acid, C6-8 neo was 553.7 mg/kg.

Repeated dermal application (400 or 2800 mg/kg daily for a total of 10 applications) of undiluted 2,2-dimethyloctanoic acid generally produced irritation at the low dose and fissuring at the high dose (Hazleton, 1964c). Slight to moderate erythema, atonia and desquamation were seen at the low dose. At the high dose, skin irritation consisted of moderate erythema, moderate to severe atonia, and desquamation with fissuring. No signs of systemic toxicity were attributed to 2,2-dimethyloctanoic acid. Therefore, the NOAEL for systemic toxicity following subchronic dermal application of 2,2-dimethyloctanoic acid was 2280 mg/kg.

In summary, Neoacids C5-C28 have a low order of subchronic toxicity. In addition, they display a consistent pattern of subchronic toxicity in that the NOAEL for systemic toxicity increases in a predictable pattern from the low to the high molecular weight end of the category. Therefore, Neoacids C5-C28 do not require further testing to assess subchronic toxicity.

Developmental Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethyloctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
DEVELOPMENTAL ORAL - RAT	RA	RA	NOAEL maternal = 250 mg/kg NOAEL fetal = 250 mg/kg NOAEL (isooctanoic) maternal = 400 mg/kg NOAEL fetal = 800 mg/kg NOAEL (isooctanoic acid) = 7500 ppm in diet	NOAEL parental = 1500 ppm in diet NOAEL F1 = 1500 ppm NOAEL F2 = 1500 ppm	NOAEL (isononanoic acid) = 1200 ppm in diet	RA

The potential for developmental toxicity of Neoacids C5-C28 can be assessed by evaluating the available data on neoacids as well as by comparison to the data on isoacids and structure-teratogenicity relationships. The available developmental toxicity data on neoacids indicate that they are not selective developmental toxicants. A developmental toxicity study conducted on Carboxylic acid, C6-8 neo produced a NOAEL of 250 mg/kg for both maternal and fetal effects (EBSI, 1986). Carboxylic acid, C6-8 neo was not a selective developmental toxicant in this study. In a 3-generation reproduction study with 2,2-Dimethyloctanoic acid, developmental effects were not observed in either the F1 or F2 offspring (EBSI, 1968). This study produced a NOAEL of 1500 ppm (in diet) for the maternal, F1, and F2 generations.

Additional developmental toxicology data are available for isoacids, which are isomers of the neoacids. The isoacids are aliphatic carboxylic acids that have saturated branching structures. Isooctanoic acid was tested for developmental toxicity in female rats at doses of 0, 200, 400, and 800 mg/kg/day during gestation days 6 - 15 (EBSI, 1995). At 800 mg/kg/day, maternal toxicity was observed; however, there were no effects at 400 mg/kg/day. There were no biologically significant developmental effects in this study. The no-observable-adverse-effect level (NOAEL) for maternal toxicity was 400 mg/kg/day and for developmental toxicity was 800 mg/kg/day.

In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999). In the parental generation, there were no treatment-related effects on survival, organ weights, or reproductive function. In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was conducted on isononanoic acid (EBSI, 1998). Rats were administered the test material in the diet at doses of 0, 600, 1200, 2500, and 5000 ppm. There were no treatment-related effects observed on mating, fertility, fecundity, or gestation indices or during sperm analysis. Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

Further support for the evaluation of the potential of neoacids to be developmental toxicants comes from an analysis of the structure activity relationships that affect teratogenicity. A structure-teratogenicity analysis of carboxylic acids concluded that aliphatic acids, which have a dimethyl substitution at the C-2 position, are not developmental toxicants (Di Carlo, 1990). Furthermore, the structural requirements for carboxylic acid teratogenicity require an alpha hydrogen and a free carboxylic group. Since the neoacids are defined by their trialkyl substitution at the alpha carbon, there is no alpha hydrogen. In addition, steric hindrance of the carbonyl group by the quaternary center of the alpha carbon inhibits reactions.

In conclusion, the available test data on neoacids and their isomers, as well as the structure-teratogenicity relationship for aliphatic acids, provide sufficient information for a screening-level assessment of the developmental toxicity of neoacids. Based on these analyses, neoacids are not considered to be selective developmental toxicants and no further testing is proposed.

Reproductive Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethylo ctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
REPRODUCTIVE ORAL - RAT	RA	RA	NOAEL (isooctanoic acid) = 7500 ppm in diet	NOAEL parental = 1500 ppm in diet NOAEL F1 = 1500 ppm NOAEL F2 = 1500 ppm	NOAEL (isononanoic acid) = 1200 ppm in diet	RA

The available reproductive toxicity studies and developmental toxicity studies prove adequate to support a screening-level hazard assessment for the reproductive toxicity potential of Neoacids C5-C28. These data support the conclusion that the Neoacids C5-C28 are not selective reproductive toxicants.

In a modified three-generation reproduction study, rats were exposed to 100, 500, or 1500 ppm 2,2-dimethyloctanoic acid in the diet (approximately 5, 25 and 75 mg/kg/day, respectively) (EBSI, 1968). No significant effects were observed in survival, appearance, behavior, or reproductive performance of the parents. No adverse effects were demonstrated in offspring on growth, appearance, or behavior. No treatment related effects were observed at gross or microscopic pathology. The NOAEL in this study was greater than 1500 ppm. The data indicate that 2,2-dimethyloctanoic acid is not a reproductive toxicant.

In a one-generation reproductive toxicity range-finding study, rats were exposed to isooctanoic acid at dietary levels of 1000, 5000, 75000, or 10,000 ppm (EBSI, 1999). In the parental generation, there were no treatment-related effects on survival, organ weights, reproductive function, or sperm indices. In the offspring, there were no treatment-related effects on survival, developmental landmarks, or any significant findings in postmortem evaluations. Statistically significant decreases in the mean offspring body weights of males and females were observed at 10,000 ppm. The high dose also resulted in a suppression of body weight gain in the adult females. Thus, the NOAEL for both parental and offspring effects was 7500 ppm.

A one-generation reproduction study was also conducted on isononanoic acid (EBSI, 1998). Rats were administered the test material in the diet at doses of 0, 600, 1200, 2500, and 5000 ppm. There were no treatment-related effects observed on mating, fertility, fecundity, or gestation indices or during sperm analysis. Evidence of maternal toxicity included decreased body weights and increased liver weights in the 2500 and 5000 ppm dose groups. In the offspring, reduced survival indices were noted in the 5000 ppm dose group, and reduced body weights were noted in the 2500 and 5000 ppm dose groups. The NOAEL for both maternal and offspring effects in this study was 1200 ppm.

In summary, these data prove adequate to support a screening level assessment of the reproductive toxicity of Neoacids C5-C28. Furthermore, these data indicate that Neoacids C5-C28 have a low order of reproductive toxicity.

D. <u>Aquatic Toxicity</u>

The neoacid products ranging from Propanoic acid, 2,2-dimethyl- to fatty acids, C9-13 neo, have been shown to produce an expected increasing level of acute toxicity to freshwater fish and invertebrates. This is based on data from the literature that are used to read across to selected neoacid products in this test plan and company data specifically for products in this category. Although there are insufficient data to confirm that a similar pattern of alga toxicity exists, based on the fish and invertebrate data, a similar increasing level of toxicity is expected from the lower to higher carbon numbered products. Proposed testing will develop the data needed to confirm this expectation. Based on the existing data, products in the Neoacids (C_5-C_{28}) Category demonstrate a low to moderate degree of aquatic toxicity from the low to high carbon numbered products, respectively.

Fish Acute Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C6-8)	2,2-Dimethyl-octanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
FISH ACUTE TOXICITY (96-hour, mg/L)	380	RA	630*	37.2	TESTING PROPOSED	RA

RA read across * Data are for a C7 branched and linear aliphatic acid product that does not contain a quaternary carbon, but is used to read across to a C6-8 neoacid product

Acute experimental fish toxicity tests are reported for Rainbow Trout (*Oncorhyncus mykiss*) and Goldfish (*Carassius auratus*). The results show that a C5 neo acid, C7 linear and branched aliphatic acid (used as read across to the C6-8 neo acid), and C10 neo acid products demonstrate that these products have a potential to cause acute fish toxicity (96-hour LC50) in the range of 630 to 37.2 mg/L.(Bridie 1979, EBSI 1993c, EBSI 1996b). The C9-13 neoacid, and the C9-28 neoacid products are not characterized. Therefore, to adequately assess the potential toxicity of the Neoacids (C_5-C_{28}) Category to fish, an acute toxicity test with the fatty acids, C9-13, neo, product will be conducted. The data from this study will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by the C10 neoacid product.

Invertebrate Acute Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C7)	2,2-Dimethyloctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
***DAPHNID* ACUTE TOXICITY (48-hour, mg/L)**	203	RA	138	47.1	TESTING PROPOSED	RA

RA read across

Acute experimental toxicity studies are reported for the Daphnid (*Daphnia magna*). The results show that a C5 neo acid, C7 linear and branched aliphatic acid (used as read across to the C6-8 neo acid), and C10 neo acid product have the potential to cause acute toxicity (48 hour EL50 or EC50) in the range of 203 to 47.1 mg/L (EG&G 1977a, EG&G 1977b, EBSI 1993a). The C9-13 neoacid, and the C9-28 neoacid products are not characterized. Therefore, to adequately assess the potential toxicity of the Neoacids (C_5-C_{28}) Category to the Daphnid, an acute toxicity test with the fatty acids, C9-13, neo, product will be conducted. The data from this study will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by fish and invertebrate toxicity data for the C10 neoacid product.

Alga Toxicity

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C7)	Carboxylic acid, C6-8 neo (C6-8)	2,2-Dimethyl-octanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
ALGA TOXICITY (96-hour, mg/L)	TESTING PROPOSED	RA	6.5 (2)	RA	TESTING PROPOSED	RA

(1) biomass
(2) growth rate
RA read across

An acute experimental toxicity value is reported for the freshwater alga (*Selenastrum capricornutum*) for a C7 linear and branched aliphatic acid product that is used as read across data to the C7 neoacid. This result shows that a C7 acid product has the potential to cause toxicity (72 hour EC50) at a concentration of 6.5 mg/L, based on alga growth rate (EBSI 1993b). Although there are no data for the remaining neoacid and neoacid ester products, overall, they are expected to exhibit a range of toxicity that falls above and below the value for the C7 aliphatic acid product. To adequately assess the potential toxicity of the Neoacids (C_5-C_{28}) Category to an alga, toxicity tests with a C5 neoacid and fatty acids, C9-13, neo, product will be conducted. The data from the fatty acids, C9-13, neo, product will be used to read across to the fatty acids, C9-28, neo, product. Comparable toxicity is expected for these two products because the higher molecular weight fatty acid components in the C9-28 neo acid product have extremely low water solubilities and do not have the potential to be in solution at effect causing levels, unlike the lower molecular weight components whose water solubilities are sufficient to cause an effect as demonstrated by the C10 neoacid product.

E. Environmental Fate

Biodegradation data are available for three neoacid products. They show that neoacid products do not have the potential to biodegrade to a great extent within a standard 28-day test duration.

Although there is some information on photodegradation and fugacity, a complete data set to adequately characterize the neoacid products does not exist. Chemical equilibrium models are used to calculate fugacity, which describes the potential of a chemical to partition in the environment. These data can only be calculated. Preliminary information for selected component chemicals of products in the Neoacids (C_5-C_{28}) Category suggests that these products are expected to partition primarily to water and soil. However, their fate in air is of environmental interest (this is discussed below under photodegradation). In addition, the majority of the component chemicals in these products have relatively low K_{ow} values, which suggests that they will not tend to partition to suspended organic matter in air and precipitate to aquatic and terrestrial environmental compartments to a significant extent.

Biodegradation

TEST	Propanoic acid, 2,2-dimethyl- (C5)	Propanoic acid, 2,2-dimethyl-, methyl ester (C6)	Carboxylic acid, C6-8 neo (C6-8)	2,2-Dimethyloctanoic acid (C10)	Fatty acids, C9-13 neo (C9-13)	Fatty acids, C9-28 neo (C9-28)
28-Day Aerobic Biodegra-dation Test	24.1 %ThOD	RA	44.0 %ThOD	11 % ThOD	2.3 % ThOD	RA

RA read across
* data developed using an acclimated inoculum

The existing biodegradation data for the neoacids products suggest that these products will not degrade rapidly in the environment. Four products have been tested and they exhibited an extent of biodegradation that ranged from approximately 2 to 44% after 28 days incubation (EBSI 1996a). These data were generated using a closed system with non-acclimated inocula. The test systems were continuously stirred, which is recommended when evaluating mixtures with several components, some of which have minimal water solubility.

Photodegradation – Photolysis

Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. Simple chemical structures can be examined to determine whether a chemical has the potential for direct photolysis in water. First order reaction rates can be calculated for some chemicals that have a potential for direct photolysis using the procedures of Zepp and Cline (Zepp, 1977). UV light absorption of the chemical components in this category will be evaluated to identify those having the potential to degrade in solution. For those compounds with a potential for direct photolysis in water, first order reaction rates will be calculated. A technical document will be prepared that summarizes the results of information developed for this endpoint.

Photodegradation – Atmospheric Oxidation

Photodegradation can be measured (US EPA, 1999a) (EPA identifies OECD test guideline 113 as a test method) or estimated using models accepted by the EPA (US EPA, 1999b). An estimation method accepted by the EPA includes the calculation of atmospheric oxidation potential (AOP).

Atmospheric oxidation as a result of hydroxyl radical attack (OH-) is not direct photochemical degradation, but rather indirect degradation. AOPs can be calculated using a computer model. Neoacid products, such as those in the Neoacid (C_5-C_{28}) Category, have a lower potential to volatilize to air. In air, these chemicals may undergo reaction with photosensitized oxygen in the form of ozone and hydroxyl radicals.

The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPIWIN, 1999) is used by OPPTS (Office of Pollution Prevention and Toxic Substances). This program calculates a chemical half-life based on an overall OH- reaction rate constant, a 12-hr day, and a given OH- concentration. This calculation will be performed for the representative chemical components in the Neoacids (C_5-C_{28}) Category and summarized in robust summaries for this group of products.

Stability in Water (Hydrolysis)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Neely, 1985). Stability in water can be measured (US EPA, 1999a) (EPA identifies OECD test guideline 111 as a test method) or estimated using models accepted by the EPA (US EPA, 1999b).

All of the chemical structures included in this category are neoacids with the exception of propanoic acid, 2,2-dimethyl-, methyl ester (C6 neoacid methyl ester), which is a carboxylic acid ester. The neoacid products are not expected to hydrolyze at a measurable rate. A technical document will be prepared that discusses the nature of the chemical bonds present and the potential reactivity of this group of chemicals with water. The computer model Hydrowin version 1.67 (EPIWIN 1999) will be used to calculate the potential hydrolysis rate for the C6 neoacid methyl ester. This information will be summarized in robust summaries for this group of products.

Chemical Transport and Distribution In The Environment (Fugacity Modeling)

Fugacity based multimedia modeling can provide basic information on the relative distribution of chemicals between selected environmental compartments (i.e., air, soil, sediment, suspended sediment, water, biota). The US EPA has acknowledged that computer modeling techniques are an appropriate approach to estimating chemical partitioning (fugacity is a calculated endpoint and is not measured). A widely used fugacity model is the EQC (Equilibrium Criterion) model (Mackay, 1996). EPA cites the use of this model in its document titled *Determining the Adequacy of Existing Data* (US EPA, 1999a), which was prepared as guidance for the HPV Program.

In its document, EPA states that it accepts Level I fugacity data as an estimate of chemical distribution values. The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent of chemical partitioned to 6 compartments (air, soil, water, suspended sediment, sediment, biota) within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical is likely to partition.

The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment. This model will be used to calculate distribution values for representative chemical components identified in products in this category. A computer model, EPIWIN – version 3.02 (EPIWIN, 1999), will be used to calculate the properties needed to run the Level I EQC model. This information will be summarized in robust summaries for this group of products.

IV. <u>TEST PLAN SUMMARY</u>

ExxonMobil Chemical Company believes that the Neoacids C5-C28 Category of chemicals should be further examined in the following manner:

- Conduct Ames assays on Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and 2,2-dimethyloctanoic acid (CAS# 26898-20-8) to evaluate the mutagenic potential of Neoacids C5-C28.
- Conduct mouse micronucleus assays Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and 2,2-dimethyloctanoic acid (CAS# 26898-20-8) to evaluate the clastogenic potential of Neoacids C5-C28.
- Calculate physicochemical data as described in the EPA document titled, *The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program* for selected chemical components of the neo acid products in this category. Provide measured data for selected products where readily available.
- Prepare a technical discussion on the potential of neo acid products in this category to photodegrade. Calculate AOP values for selected chemical components of neoacid products in this category.
- Prepare a technical discussion on the potential of neo acid products in this category to hydrolyze. Calculate the hydrolysis rate of Propanoic acid, 2,2-dimethyl-, methyl ester (CAS# 598-98-1).
- Calculate fugacity data for selected chemical components of neo acid products in this category.
- Conduct a fish acute toxicity test with Fatty acids, C9-13 neo (CAS# 68938-07-8).

- Conduct a Daphnid acute toxicity test with Fatty acids, C9-13 neo (CAS# 68938-07-8).
- Conduct algal toxicity tests with Propanoic acid, 2-2-dimethyl- (CAS# 75-98-9) and 2,2-dimethyloctanoic acid (CAS# 26898-20-8).

ExxonMobil Chemical Company believes the thorough evaluation of the strategic anchor studies, the development of selected information and data, and the overall robustness of the final screening data set for the Neoacids C5-C28 Category complies with the objectives of the HPV volunteer testing program.

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Table 3. Assessment Plan for the Neoacids C5-C28 Category Under the Program. (Robust summaries for existing studies are submitted separately.)

	Human Health Effects						Ecotoxicity				Environmental Fate			
Stream Description	**Acute Toxicity**	**Genetic Point Mut.**	**Genetic Chrom.**	**Sub-chronic**	**Develop-mental**	**Reproduction**	**Acute Fish**	**Acute Invert.**	**Algal Toxicity**	**Physical Chem.[1]**	**Photo-deg.**	**Hydro-lysis**	**Fugacity**	**Biodeg.**
Propanoic acid, 2,2-dimethyl-	A	T	T	A	RA	RA	A	A	T	CM/M	CM	CM	CM	A
Propanoic acid, 2,2,-dimethyl-, methyl ester	RA	RA	RA	RA	RA	RA	RA	RA	RA	CM/M	CM	CM	CM	RA
Carboxylic acid, C6-8 neo	A	RA	RA	A	A	A	A	A	A	CM/M	CM	CM	CM	A
2,2-Dimethyloctanoic acid	A	RA	RA	A	RA	A	A	A	RA	CM/M	CM	CM	CM	A
Fatty acids, C9-13 neo	RA	RA	RA	RA	RA	A	T	T	T	CM/M	CM	CM	CM	A
Fatty acids, C9-28 neo	RA	T	T	RA	RA	RA	RA	RA	RA	CM/M	CM	CM	CM	RA

1 Measured data for selected physicochemical endpoints will be identified in conjunction with calculated data to characterize this category.

A Adequate existing data available
TD Technical Discussion proposed
RA Read Across (see Sec. III.B)
CM Computer Modeling proposed
T Testing proposed
M Measured data where available
NA Not Applicable